Report on genetic testing for late onset disorders : September 1998 / Advisory Committee on Genetic Testing.

ADVISORY COMMITTEE ON GENETIC TESTING

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Dear Colleague,

CONSULTATION - DRAFT REPORT ON GENETIC TESTING FOR LATE ONSET DISORDERS

This letter seeks views on a draft report on testing for late onset genetic disorders prepared by the Advisory Committee on Genetic Testing (ACGT). ACGT hopes that the report will provide a useful reference for all those currently providing genetic testing for late onset disorders and those considering developing such a service.

Genetic testing for late onset disorders such as Huntington's Disease has for many years been a core service offered by NHS Genetics Centres and other providers of genetic services. The level of provision and proficiency of such services is high. There are increasing demands on existing services, and as the number of disorders that can be tested for grows, for new ones. For this reason ACGT have in this draft report considered those genetic disorders that normally do not become evident until adulthood and some of the issues that surround them.

We outline our thoughts on the special features of genetic tests for such disorders, the current service provision, and the validity of such tests. In addition we set out our views on issues that all service providers need to consider when providing testing services for late onset disorders. These include, the known error and failure rates of tests, requirements for laboratories performing tests, information and support needs of those tested, requirements for consent to testing, statements on prenatal testing and testing of children and adolescents, and the use of test results in research studies.

Also included for completeness are brief statements on population screening, diagnostic genetic testing and genetic susceptibility, although we hope to return to these subjects in a fuller manner in future ACGT reports.

ACGT regard it as important that their reports are widely understood and accepted by the public, industry and clinicians. This consultation represents an important means of inviting views on our views and proposals, and I would be grateful for your comments on each of the draft's sub-sections. In preparing the draft report the Committee hopes that it will prompt a number of responses. We will take these into account when preparing a revised draft and deciding how best to move ahead.

If you have any comments on the Code of Practice please send them, by Friday 16 January 1998, to Mark Noterman at the address above.

Yours faithfully,

JOHN POLKINGHORNE KBE FRS

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PREFACE

The Advisory Committee on Genetic Testing is a non-statutory advisory committee reporting to UK Health Ministers on developments in genetic testing.

The Advisory Committee's membership includes representatives from consumer groups, industry, clinicians, philosophers, academics and scientists. It works through meetings of the full committee, or where appropriate through Sub-Groups, taking advice when necessary from invited experts. ACGT's work is funded by UK Health Departments and it is supported by a secretariat based in the Department of Health, London.

ACGT's first report, the Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public, was published in September 1997.

ACGT consulted widely on the content of this, our second report, in late 1997, and agreed this published version in March 1998. We are grateful for the valuable contributions of all those who so helpfully responded to the consultation process.

Rev Dr John Polkinghorne KBE FRS
Chairman, Advisory Committee on Genetic Testing
Cambridge

March 1998

FOREWORD

The Advisory Committee on Genetic Testing (ACGT)

ACGT was established, under the Chairmanship of the Rev Dr John Polkinghorne KBE FRS in 1996. A full list of ACGT's members is at Annex A. ACGT's remit covers the whole of the United Kingdom.

ACGT's Terms of Reference are:

(i) to provide advice to Ministers on developments in testing for genetic disorders;

(ii) to advise on testing individuals for genetic disorders, taking account of ethical, social and scientific aspects; and

(iii) to establish requirements, especially in respect of efficacy and product information, to be met by manufacturers and suppliers of genetic tests.

ACGT's Secretariat is provided by the Department of Health. That Department, the Department of Trade and Industry and the Human Genetics Advisory Commission (a separate non-statutory advisory body, of which the Chairman of ACGT is a member) send observers to ACGT's meetings.

Late Onset Disorders and Genetic Testing

Late Onset Disorders are those disorders that normally become symptomatic in adult life. During their inquiry into human genetics the House of Commons Select Committee on Science and Technology[2] said that:

> "People coming forward to be tested for a late onset condition must first be given extensive counselling about both the medical and social implications of a positive result. There needs also to be adequate provision for follow up counselling and support."

Because of these concerns and the increasing emphasis given to testing for late onset diseases by researchers, industry and patient support groups, ACGT recognised, at their first meeting, the high priority that should be given to consideration of issues raised by genetic testing for late onset disorders. ACGT therefore at its second meeting established a Sub-Group, chaired by Professor Peter Harper, to prepare this report.

Genetic testing may help in diagnosis by establishing the cause of symptoms or of a disorder. It may also indicate that a person will develop a disorder in future; or that they are a carrier of a condition, so that although they will not themselves be affected,

they may have affected children. Tests for genetic susceptibility to common diseases such as cancer, heart disease and diabetes are being developed and an increasing range of tests can be anticipated. In the UK genetic testing services are most often provided through the National Health Service[1], and most people requiring these services obtain them by referral from their general practitioner. Consultant-led NHS genetics services are available throughout the UK, and ACGT recognises the importance and achievements of these services. Regional Genetics Centres throughout the UK can supply information to clinicians and members of the public on the range of services they provide, and their addresses and contact telephone numbers are listed at Annex B.

In its first report ACGT recognised a limited role for the provision of genetic testing services direct to the public ie. outside of the setting of NHS genetics services, however it saw such testing being centred on tests which determine carrier status for inherited recessive disorders, where such status carries no significant direct health implications for the carrier individual (eg cystic fibrosis). ACGT considered that provision of such testing poses fewer difficulties than provision of testing for inherited dominant and X-linked disorders, for adult onset genetic disorders regardless of inheritance [the late onset disorders of this report] or for the genetic component(s) of multifactorial or acquired diseases.

ACGT continues to regard the provision of tests for late onset disorders as more problematic than other genetic tests and believes that such tests are best conducted in a clinical setting.

Conclusion

ACGT recognises that clinicians in the NHS and private practice have essential roles to play in the provision of genetic testing services for late onset disorders. ACGT wishes to ensure that such testing is delivered with the best interests of those tested in mind and that such testing is only performed in appropriate circumstances and with suitable information and genetic consultation available.

The Government has a public health and consumer protection role to encourage good practice in the provision of genetic testing. These issues are covered in this report.

It is the aim of ACGT, by means of this report, to set out the issues that need to be considered by clinicians before considering offering genetic testing for late onset disorders and during the provision of such testing. ACGT hopes that it may also be of interest to those being tested, patient support groups, testing laboratories, and general medical practitioners and other health care professionals with an interest.

Definitions used in this Report

Genetic Testing - Testing to detect the presence or absence of, or change in, a particular gene or chromosome.

A. Diagnostic Genetic Testing

Use of genetic testing in a symptomatic individual to aid in the diagnosis, treatment and management of that individual.

B. Predictive Genetic Testing

i. Presymptomatic Testing - Testing primarily carried out in healthy or asymptomatic individuals to provide definitive information about that individual's future health; such a test result will give the individual a high likelihood of developing the disorder or of excluding it. Predictive testing is most frequently used in late onset autosomal dominant disorders such as Huntington's Disease.

ii. **Susceptibility Testing** - Testing which provides information abut the genetic component in a multifactorial disorder (see below).

Late Onset Disorder - Disorders that normally become symptomatic in adult life. Inherited disorders which have effect at birth or during childhood are excluded.

Multifactorial - Many disorders have a genetic component that is not the sole cause, but which works alongside other often environmental or lifestyle factors in determining a disease outcome. Multifactorial disorders include many cancers, cardiovascular diseases, some forms of diabetes etc.

Mutation - The change in a gene or chromosome that causes a disorder or the inherited susceptibility to a disorder. Only heritable mutations are considered in this report.

Genetic Counselling - A process by which information is imparted to those affected by, or at risk of a genetic disorder. It includes information on the nature of the disorder, the size and extent of genetic risks, the options, including genetic testing, that may help clarify the risks, and the available preventive, supportive and therapeutic measures. In the context of genetic testing it may include responding to the concerns of individuals referred and their families, discussing the consequences of a test, and help to choose the optimal decision for themselves, but not determining a particular course of action.

Autosomal Dominant Disorders - Disorders where inheritance of a mutation from one parent only (or arising anew during egg or sperm formation) can be sufficient for the person to be affected. Important dominant disorders in the UK include familial hypercholesterolaemia, Huntington's Disease, adult polycystic kidney disease and familial adenomatous polyposis.

Autosomal Recessive Disorders - Disorders, where for a person to be affected, a mutation has to be inherited from both parents. Such parents are usually unaffected carriers because they only have a single copy of the mutant gene. Recessive disorders commonly have onset in childhood and include cystic fibrosis, sickle cell disease and thalassaemia. Haemochromatosis is an example of a late onset recessive disorder.

X-Linked Disorders - Disorders due to a mutation on the X chromosome. X-linked disorders usually only affect males, but the disorders can be transmitted through healthy female carriers.

GENETIC TESTING FOR LATE ONSET DISORDERS

BACKGROUND

Late onset disorders

Many serious disorders have their clinical onset in adult life, without preceding symptoms or other features in childhood. Late onset disorders may be progressive and seriously disabling; in high economy societies they account for a considerable proportion of mortality and serious ill health, often affecting those with major employment and family responsibilities. This document deals with disorders that normally do not manifest until adult life including those (like many variable genetic disorders) that may occasionally become symptomatic in childhood.

The genetic basis of late onset disorders

Many late onset disorders have long been recognised to run in families to a certain extent, even when clear environmental factors can be identified, but it is only recently that it has become possible to identify specific genetic factors involved. For the purpose of this report, two broad groups can be recognised:

(a) Disorders following a clear cut pattern of inheritance, where alteration of a single gene is largely responsible for the disorder and where risks to relatives may be high. Established NHS genetics services have principally been concentrated on this group of disorders. "Dominant" inheritance, giving a 50% genetic risk to offspring of an affected person, is a frequent inheritance pattern in this group. The occurrence of new genetic mutations means that a significant proportion of such individuals may not have a family history of the condition, though their offspring will still be at high risk. These disorders are usually relatively uncommon, but they are numerous (several thousand), giving a large amount of disease overall and a considerably larger number of relatives at high risk. Examples include adult polycystic kidney disease (one of the main causes of chronic kidney failure), Huntington's disease (HD) a serious, progressive brain degeneration and familial polyposis of the colon (an inherited form of bowel cancer) and a number of rare familial forms of cancer. A few late onset disorders follow "recessive" inheritance eg. haemochromatosis. Here, if two carriers of the altered gene have a child there is a 25% risk of an affected offspring.

(b) Disorders showing a significant genetic contribution but where family patterns are rarely clear cut, risks to relatives are relatively low and less clear cut than in group 1, and where the disorder is often the result of important environmental influences interacting with genetic factors. Examples include

diabetes, coronary heart disease, schizophrenia and diseases of the elderly eg Alzheimers.

In addition to these two broad groups, a number of common late onset disorders (eg breast cancer) are now recognised as containing a minority of cases following a clear pattern of single gene inheritance, which were not clearly distinguishable from others until the isolation of the specific genes involved.

New developments in genetics

New techniques in genetics have made it possible to identify and isolate specific genes involved with important human disorders, including an increasing number of those with late onset. This is already having important consequences, including:

(a) Greater understanding of the disease process by identifying the nature of the protein normally produced by the gene, its relation to other body processes and how changes in the gene result in disease. Since many late onset disorders have been poorly understood, this increased understanding is of great importance in the development of future treatments. Identification of specific genes is also improving our knowledge of the variability and natural history of the disorders.

(b) Genetic testing is now frequently feasible, based on changes in the specific genes involved, or on tracking the family pattern of normal variations in, or adjacent to, them. This may give possibilities for accurate risk prediction for relatives.

(c) If specific changes (mutations) in a gene can be identified as causally related to a disease, they could be used in diagnosis of possibly affected individuals or in population screening, even in the absence of a family history of the disorder.

Difference between genetic tests and other tests in medical practice

Most medical tests are able to detect evidence of a disease process that is already present and help to resolve its nature. Some (e.g. sensitive imaging techniques) may detect changes in those at risk before symptoms occur, but they still reflect an early stage of the pathological process. Genetic tests, particularly those based on analysis of the genetic material itself (DNA), differ in a number of important ways:

(a) Since the DNA that a person inherits and passes on remains largely unchanged throughout life, genetic testing for inherited disorders, based on analysis of DNA can potentially be done at any point from conception to old age.

(b) The presence or absence of an abnormality in a genetic test is unaffected by whether the individual has symptoms of the disease or not.

(c) Since DNA is present in most body cells, any tissue sample can be used for a test for inherited disorders, not just that affected by the disease. Blood or mouthwash samples are examples.

(d) DNA is extremely stable, and can be analysed using stored samples taken for other purposes (eg newborn screening or surgical samples) or samples from individuals no longer living.

(e) Human genetic testing for inherited disorders differ from most other clinical tests which only involve a single individual, because they may also reveal important information about relatives and can have a great impact upon families. An adult with no risk of developing an illness may seek advice on their chance of passing on a mutation to their children.

(f) Another distinctive feature of some genetic tests is their power to predict the potential future health of the individual. This possibility to foretell the future with scientific confidence is a totally new feature in medical tests, and has particular significance in relation to employment and insurance.

(g) Genetic testing raise serious issues, and some of these may be more complex than those faced in other clinical areas. The test result, which has implications for the family as well as the tested individual, may cause anxiety or alleviate concerns in an otherwise healthy individual. Therefore the consultation before and after a genetic test, to explain the implications and consequences of the result, may be different from that needed in many other types of medical test or treatment. Persons tested, and possibly their families, need to understand before the tests are performed what the results may mean for them. Confidentiality must be appropriately protected but the probable implications for family members need to be understood by the person tested.

(h) An abnormal genetic test result may have a powerful effect on a person's perception of the nature of the disease and whether it can be treated or prevented.

There will be a progressive blurring between genetic testing and other testing in clinical use which are can be used as less direct markers for genetic disorders. eg. serum lipids in familial hypercholesterolaemia. Therefore the issues listed above for genetic testing will need to be considered in the application of other tests, and many of the ethical and other issues listed are relevant to other areas of medical and surgical consultation and practice.

Features of genetic testing especially relevant to late onset disorders

All the above points are important, but for late onset disorders, they result in several situations which do not usually arise so prominently in childhood genetic diseases:

(a) Since the genetic change underlying a late onset disorder can be identified at any age, there may be an interval of years or even decades between a healthy individual being tested and the onset of the disease. It is also being increasingly recognised that even for some disorders following a clear cut inheritance pattern, a proportion of those showing the genetic change may remain entirely healthy.

(b) The result of a genetic test rarely gives an individual information on timing of onset or likely severity that is sufficiently precise to be helpful.

(c) Because late onset disorders may interfere little with reproduction, in addition to those actually affected there will be many relatives who are healthy but at risk of having the genetic change and many of those at risk may not be aware of it.

Practical experience of genetic testing for late onset disorders

This is currently limited, since most of the disorders where genetic testing initially became possible, were those of childhood onset. Significant experience is limited to a small number of genetic disorders, notably HD and some forms of familial cancer. For the common "multifactorial" disorders there is almost no experience in a service setting since the range of specific genes and environmental factors involved has rarely been sufficiently established to allow accurate prediction.

The experience from HD, a disorder giving severe, progressive physical disability and often mental deterioration, is of particular value. Genetic testing has been available for 10 years, different centres world-wide have used thorough and comparable protocols, capable of evaluation; genetic testing was introduced in expert centres

cautiously, in conjunction with guidelines supported by the lay groups, with full information and support for those tested. Over 2,000 individuals at risk for HD had been tested in Britain by the end of 1996.

It is thus not surprising that the experience of HD has been used as a model for genetic testing in other late onset disorders and that it has identified many of the issues detailed later in this report. Data are now becoming available from some forms of familial cancer but there is an urgent need for such data to be collected on other late onset disorders.

Current service provision

Established medical genetics services, both laboratory based and clinical, have been centred on clearly defined genetic disorders (late onset as well as childhood) that are mostly relatively uncommon, even though in aggregate they amount to a large burden of serious disease. Most genetic testing is carried out within the NHS and is based upon regional genetics centres which serve groups of health authorities. Other genetic testing services may be provided by general practitioners, clinicians in private practice, by such specialities as oncology and haematology and within research settings; many of these tests may be carried out in collaboration with regional genetics centres. UK genetics services are characterised by a number of important features that can be utilised to advantage in the appropriate development of genetic testing services. These include:

(a) Bases in regional centres, serving relatively large populations (commonly 2 - 5 million people), but allowing personal links with referring clinicians in the region.

(b) Extremely close links between laboratory and clinical genetics services, allowing planned service development, appropriate clinical input to laboratory tests results, and the involvement of clinical geneticists and genetic nurse specialists in genetic counselling, pre-test preparation and other aspects of the overall service.

(c) Close collaborative links across the UK and beyond, permitting highly specialised services for rare disorders that can only be economically provided in a very few centres. In addition many genetic tests will be developed through additional funding from commercial organisations.

(d) Strong links with academic medical genetics units, allowing new basic research findings and technology to be introduced quickly into service provision, and encouraging more applied Research and Development activities. This is an essential feature of such a rapidly changing field as genetics.

(e) Awareness of the important issues outlined later in this report means that genetics services are an important safeguard against the inappropriate or excessive use of genetic testing. They are also the main source of education for other clinicians who are increasingly the main requesters for tests.

(f) Because of this increasing use of genetic testing by all clinical disciplines it is important that the skills learnt by many clinical geneticists, not only in relation to collecting and analysing genetic data but also such general aspects as empathy, information giving, acknowledgement of family issues and confidentiality, are taught within the medical school curriculum.

Regulation of Genetic Tests and Reagents

The proposed European *In Vitro* Diagnostics Directive is presently undergoing negotiations in the Council of Ministers' Economic Questions Working Group. It is a single market initiative with the primary intention to remove technical barriers to trade between Member States. On completion of the Directive and its acceptance, regulations will come into force in each member state of the European Union which will in the future **require** *in vitro* diagnostic medical devices to be CE-marked in declaration of conformity with the Essential Requirements of the Directive in order to be placed on the market. These essential requirements are likely to address safety aspects, require that products meet the performance claims made by the manufacturer, and require that they do not adversely affect the health and safety of a patient, user or other persons. Genetic tests, and components of them, which are placed on the market will in the future be regulated in this way. Such regulations are not intended to be the vehicle for addressing broader aspects surrounding the use of IVDs, such as ethical issues or their use in conjunction with counselling.

ISSUES ARISING IN PREDICTIVE GENETIC TESTING FOR LATE ONSET DISORDERS

The rapidly increasing number of genes identified for late onset disorders, the special features of genetic testing and the particular nature of the disorders themselves, have combined to create a range of important issues that should be given careful consideration before genetic testing is offered as a service.

At present these issues arise mainly in relation to pre-symptomatic genetic testing of healthy relatives with a family history of serious late onset disorder with a clear genetic basis and commonly following dominant inheritance. The following sections deal primarily with this pre-symptomatic form of genetic testing.

Three somewhat different areas of genetic testing are dealt with separately later at Annexes A, B and C. These are: population screening for late onset disorders; the diagnostic use of genetic tests in clinically symptomatic individuals; and genetic susceptibility testing for late onset disorders involving multiple genetic and environmental factors. These three categories also raise important issues, but some are additional and specific, while our practical experience in these areas is extremely limited.

Scientific and clinical validity of the test

Scientific and clinical validity should be clearly established before any genetic test is used in clinical practice, but validity may be especially difficult to establish in late onset disorders, where those carrying the genetic abnormality will be healthy for much of their life, prior to onset.

(a) *It must be clear that the genetic change found is causally related to the disorder, before it is used as the basis for a genetic test. Validity should be based on published, peer reviewed evidence.*

Normal variation in DNA is very great and considerable data may be required before it becomes certain that a genetic change found in association with a disorder is causally related, not coincidental. In the case of linked genetic markers (surrogate markers), any possible error associated with recombination should be accurately known and be small.

(b) *The extent and limitation of the association between the test result and the disorder (false positive and false negative rates) should be accurately known.*

Even when the scientific validity of the test is clear, there may be important factors that mean the association is not absolute. There may be situations where individuals with the genetic change never develop

the disorder (e.g.: up to 10% of individuals with mutations in the BRCA1 gene involved in familial breast cancer). There may also be reasons why a proportion of individuals with a normal test result are still at risk of developing the disorder; in particular it may not be possible to test for all the known mutations in a gene, a proportion of cases may be the result of changes in a different untested gene (genetic heterogeneity), or as in breast cancer a large majority of cases have no known genetic cause. Where the test is based not on a specific change but the pattern of transmission in a family (genetic linkage), there will be a definite rate of both false positive and false negative results because of separation of the disease and marker genes (recombination) when they are passed on.

(c) *Any correlation between test result and disease severity or age at onset should be recognised, but should only be incorporated into the test result as given to the individual if it is validated and is sufficiently strong to be of use in the context of an individual result.*

When an abnormal genetic test result is obtained it usually does not allow any clear prediction of severity or age at onset, but some specific mutations are being found to be associated with severe or with less severe disease; age at onset has likewise been found to be statistically associated with the extent of the genetic change in some mutations that are variable in size, as seen in HD and myotonic dystrophy. This type of information may be extremely important to those tested, but it should only form part of the test result as given to the individual if the associations have been validated and if the information can be used in interpreting an individual result rather than an overall series.

Is the testing "service ready?"

Even when a genetic test is validated scientifically, there are further considerations that need to be established before the test can be considered as valid in a service setting, rather than in research.

The error rate and failure rate should be known to those requesting the test and those being tested.

This represents the technical or human error rate, as opposed to the inherent false positive or false negative rate. It may be influenced by the complexity or fallibility of technical procedures, by human error or (as in some prenatal tests) by cells failing to grow in tissue culture.

Laboratories undertaking genetic testing

The following issues are important, but are not specific to late onset disorders.

(a) *All laboratories providing a genetic testing service should be appropriately accredited for this as well as taking part in internal and external quality control schemes.*

All laboratories offering genetic testing services should be appropriately staffed and equipped, and should:

(i) participate in an appropriate accreditation scheme:

(ii) join an appropriate external quality assurance scheme; and

(iii) perform adequate internal quality control.

All such systems should reflect current best practice. Examples of (i) and (ii) are registration with a National Accreditation Body and conformity with the requirements of BS EN ISO 9002 (Formerly BS 5750 Part 2). Continued registration is dependent on satisfactory audits that are performed at prescribed intervals by the Accreditation body to ensure compliance with the appropriate standards, and accreditation by the Clinical Pathology Accreditation (UK) Ltd (CPA). Accreditation by CPA involves external audit to standards reflecting best professional practice for clinical laboratories.

ACGT believes that such standards are applicable to all laboratories performing genetic testing services, including those in the NHS. Some genetic disorders are so rare that only a research laboratory may be able to undertake testing. Such laboratories should only offer a service if they are able to follow expected service standards, but equally it should be made clear to those requesting testing or being tested that the research nature of the laboratory may give limitations.

The accrediting body may vary according to the nature of the genetic testing, which may be based on DNA, chromosome or biochemical analysis, but it is essential that the main requisites of a genetic testing service are addressed, regardless of the technology used.

(b) *Research laboratories should not normally be the basis for a genetic testing service; where they are, because of the rarity of the disorder or other factors it is essential that the service delivered conforms to the same standards expected in an approved service laboratory.*

If the early stage of development of the genetic test means that the field is still at the borderline of research and service, this should also be made clear, and the test should not be offered or promoted as an established service.

(c) *Genetic testing should be undertaken only by laboratories closely linked with other genetics services.*

Many general pathology and haematology laboratories use genetic techniques to investigate disease, while the detection of somatic (non-inherited) genetic changes forms an important part of laboratory analyses of tumours. Although the technology may be the same, genetic testing for inherited disorders, in particular pre-symptomatic testing, require different approaches, and should not be undertaken by general laboratories unless they form part of a specific genetic testing service, and meet the general provisions for accreditation and level of expertise appropriately.

Information needed by those being tested

The communication of various types of information outlined in this section comprises an considerable part of the process known as genetic counselling whether it is given by clinical geneticists, genetic nurse specialists or by other professionals.

(a) *Information on the disorder being tested for should be full, accurate and appropriately presented.*

While some individuals requesting predictive genetic testing for a late onset disorder will have extensive experience of the condition from their own family, others will not, or the information may be incomplete. This information is essential if individuals are to make appropriate decisions regarding testing.

(b) *Full information should be provided on the test, its consequences and limitations, and its scientific and clinical validity.*

Some individuals being tested may have inaccurate expectations as to what a genetic test can deliver in terms of removing or confirming risk, or in predicting severity or age of onset. This may also apply to some clinicians requesting testing.

(c) *Individuals should be fully informed of potential adverse consequences, such as for insurance, employment, and effects on other family members.*

Experience with genetic testing for HD and other serious late onset disorders has shown that while many individuals are well informed in advance, there are almost always significant issues that have not been already considered and which are important for them to make an appropriate decision.

(d) *Information should be provided in a clear and simple manner that is readily understandable. While written information is important, complex information should be provided face to face by an appropriately trained and experienced person.*

In genetic testing for serious late onset disorders, there are frequently complex and sensitive issues that require discussion, rather than simply provision of information. While not all such issues require involvement of specialist genetics services, these have an important role when they are complex and time-consuming, or when they involve members of the extended family. Genetic Nurse Specialists and other professionals play an important role in pre-test preparation and in post-test home visiting to ensure that necessary support is provided and that information has been received and understood. Voluntary organisations involved with genetic disorders can also be a valuable source of information for those considering genetic testing.

(e) *Individuals should be given adequate time to absorb the information provided, before a result is given.*

For serious late onset disorders such as familial cancers and HD, a two step approach has been found to be important in allowing time for reflection. Since a premium is often placed on avoiding delay in other laboratory testing situations, it is important that this time interval is protected.

Consent to genetic testing

(a) *Where an individual is able to give consent, genetic testing should only be undertaken after such consent is given. In the case of presymptomatic genetic testing of healthy individuals, written consent should always be obtained. The main purpose of consent is to provide documentary evidence that an explanation of the proposed procedure was given and that consent was sought and obtained.*

Written consent is already established practice in presymptomatic testing for HD and most other serious late onset disorders. As such testing becomes more widespread this should be a general policy. In diagnostic testing of symptomatic individuals current policy is more variable; we consider written consent desirable here also.

(b) *Consent should be specific.*

New technology may make it possible to test for many genetic diseases at one time and could generate results relating to disorders that the individual was not even aware of, a situation which should be carefully avoided. If testing is for a group of allied disorders, this should be made clear when consent is being obtained.

(c) *Where an adult is permanently incapable of giving consent (e.g. because of a learning disability) the legal position is that the decision will be made by the doctor responsible for the person's clinical care who will be guided by the best interests of the individual and will take into account, where appropriate, the views of the family or other close carers. If the incapacity is temporary, genetic testing should be delayed until consent is possible unless it is essential in the individual's therapy. (The special case of testing children is considered below).*

The issues of testing of the incapacitated are complex and in relation to genetic disorders we need to distinguish between the situation in which testing is necessary in furtherance of the individual's treatment, when it will be clearly in their best interests; where testing might be proposed essentially in the interests of furthering the diagnosis, but without implications for treatment; and where testing is predictive, with no symptoms likely to be related to the disorder being tested for.

In psychiatric practice, mental illness may result in temporary incapacity to consent and the clinician must then be guided by consideration of the individual's best interests. However, many mentally ill people retain the capacity to consent but assessment of that capacity can at times be difficult. It is important to guard against the risk of an individual giving

consent during a period of mental illness which they would have withheld had they been in normal health by ensuring that the individual fully understands the nature of the proposed test and its likely consequences and is able to balance these issues appropriately in making their decision.

(d) *Consent should be freely given, without pressure from third parties.*

There has been public concern that pressure for genetic testing for serious late disorders might come from insurers or employers, though currently there is no clear evidence of this happening directly. A more frequent and more difficult to resolve issue is that of pressure to be tested from family members. This may only be recognised when the issues are discussed before testing. Professionals involved in providing genetic testing should likewise not exert pressure and should present information in a way that permits a free choice.

Support in relation to genetic testing

(a) *Appropriate support in preparation for and subsequent to genetic testing should be considered as part of the genetic testing process.*

Genetic testing for late onset disorders may have consequences extending many years ahead and affecting multiple family members. The testing process itself may also be extremely stressful, but experience from HD and familial cancers suggests that even serious adverse results can usually be well coped with if the person tested is fully prepared and has adequate support. The likely needs for support should be considered and planned for as part of the testing process, otherwise unexpected serious problems could be generated for the individual, for family doctors and for other staff.

As much of the long-term support, follow-up and co-ordination will devolve to primary health care teams it is important that they have the mechanisms to cope with this duty. Such mechanisms include suitable record keeping of genetic tests taken, recall dates and family history data.

(b) *Purchasers should consider and cost the potential support needs of genetic tests when evaluating and commissioning genetic services.*

The cost of associated genetic counselling and related measures should be costed in addition to and separately from the laboratory aspects of a genetic test. Some genetic tests for late onset disorders, such as that for polyposis coli, will reduce later costs of investigating or treating serious diseases. The potential effects of abnormal test results in terms of long term support and medical investigations also need to be considered when the likely overall benefit of the test is being assessed.

"Over the counter" genetic testing for late onset disorders

(a) *A previous ACGT report has already recommended against such testing and we support this conclusion.*

ACGT considers that the main role for genetic testing supplied direct to the public should be limited to determination of carrier status for inherited recessive disorders in which an abnormal result carries no significant direct health implications for the customer. ACGT considers that the provision of such testing poses fewer difficulties than provision of tests for inherited dominant and X-linked disorders, chromosomal disorders, for adult onset genetic disorders regardless of inheritance, or for the genetic component(s) of multifactorial diseases including tests for somatic mutations.

The complexity of issues, both scientific and general, involved with genetic testing for late onset disorders makes "over the counter" testing inappropriate for this category of disorders.

(b) *Any medically qualified person requesting or providing genetic testing for late onset disorders should ensure that they, or another suitably qualified medical practitioner, are actively involved in the process.*

There is a possibility that medical involvement may be "token" in nature, leading effectively to a situation equivalent to "over the counter" testing. This should not be permitted.

Pre-symptomatic Genetic Testing of young children for late onset disorders

(a) *"Over the counter" genetic testing of children is not appropriate.*

This was the conclusion of the committee's previous report* and we continue to endorse this approach. The issues involved may be complex and they require professional involvement.

(b) *Any request from a person or persons with parental responsibility to professionals, for pre-symptomatic genetic testing of a young child unable to give consent, should be fully discussed in context of the particular family situation, the nature of the disorder, the possible medical or other benefits, and the implications of testing for the child and family.*

Requests for such testing are frequently part of a more general need for information and require full and sensitive discussion with a professional who can provide this; they should not be simply accepted or declined on ground of general policy. If a child is to be tested, then the consent to be given for the test by the person or persons with parental responsibility should be on the basis that it is in the child's best interest.

(c) *Presymptomatic testing of young children for disorders not currently influenced by therapy, and where onset is normally in adult life, is not recommended, though there may be special situations that are exceptions to this.*

Since young children are usually unable to give consent, it is preferable for important decisions relating to their adult life to be left to a time when they can give consent themselves, especially since it is known that a considerable proportion of adults may decline testing in such a situation. This has also been the conclusion of other bodies, such as the Clinical Genetics working group report*, the Genetics Interest Group* and the US Task force on Genetic Testing*. The situation for a particular disorder will require reassessment in the light of advances in therapy.

(d) *Where genetic tests are being used diagnostically in the context of a child with a family history of a late onset disorder showing clinical features, it is essential that these clinical features are relevant to the nature of the family disorder.*

Genetic testing is increasingly part of diagnosis in paediatric practice. Where a late onset disorder may occasionally occur in childhood, there is the risk that in a child with symptoms, these might be unrelated to the disorder in the family; this would give a real risk of inadvertent detection of the gene being present, with serious implications for later life. Many clinicians do not at present recognise this potentially dangerous situation.

Genetic testing for late onset disorders in adolescents

Requests from adolescents themselves regarding presymptomatic genetic testing for late onset disorder deserve full and sensitive discussion, taking into account the individual and their family. If the adolescent is competent to give consent but there are not clear benefits of testing, we would recommend that ideally testing be deferred until the age of majority is reached. However, the competent adolescent is entitled to make a personal decision on this matter after a full discussion and exploration of the issues.

Adolescents will vary greatly as to their emotional and mental maturity in relation to complex issues for later life. Current experience is that such requests are few but that they need full discussion with an experienced person. Pregnancy could be a special situation where testing needs to be considered.

In some late onset disorders, eg familial adenomatous polyposis, for which treatment might be possible or for which screening might detect the condition at an early enough stage for treatment to be effective there is good reason to consider early testing of adolescents. In conditions such as familial cardiomyopathy where there may be a family history of sudden death in young family members there may be benefit in carrying out predictive testing in children and adolescents. The situation for each disorder requires careful consideration.

Prenatal genetic testing for late onset disorders

Prenatal genetic testing for late onset disorders should only be undertaken in the context of full genetic counselling.

Requests for prenatal genetic testing are relatively uncommon for late onset disorders by comparison with serious childhood genetic disease. In general, requests are normally related to severe and untreatable disorders, where the individual concerned has experienced particular adverse effects of the disorder. Prenatal testing also can provide an option for those healthy individuals with an abnormal presymptomatic test result to have children free from the genetic disorder in question. There may be complex situations when a person simultaneously requests presymptomatic testing for themselves and for their pregnancy.

A particular issue arises when a couple decide to continue a pregnancy after an abnormal prenatal test result. This effectively gives presymptomatic diagnosis for the child after it is born, in contradiction to the recommendations given above. Although this may be an inevitable occurrence on occasions, full discussion in advance of prenatal testing should minimise it.

Genetic testing and results of research studies

Most genetic studies leading to isolation of a disease related gene have involved analysis of affected and unaffected family members. Research on the genes for familial cancers and HD are examples of the importance of such family studies in late onset disorders. Stored DNA samples may be available for testing long after the original study has been completed. This gives the possibility of important results being generated when the individuals concerned may be unaware of this and may not have given specific consent. In the case of late onset disorder an abnormal result may be found in healthy relatives. Such information may be available in the research laboratory and difficult questions may arise as to whether or not participants should be informed of the results.

(a) *Research studies that generate identifiable genetic test results on individuals should only be done with consent of the individuals and following approval of a designated ethical committee.*

Safeguards of this nature are particularly important since the stability of DNA creates the possibility of samples collected originally for a study with no individual implications being used subsequently to generate sensitive genetic information. Where there is a possibility of this, new consent and new ethical committee permission should be obtained, or the samples should be made completely anonymous. There may be exceptional situations where research information needs to be used, as when an individual is deceased and no further material is available, or when no service is available outside a research setting.

(b) *Individual genetic test information resulting from research studies should not be given to participants unless a clear and specific arrangement has been made at the onset. Research participants should be made aware that they will not receive genetic test information that forms part of research.*

Research information is, by its nature, provisional and the way material is collected and analysed will often make it unsuitable for service use. Where a research participant wishes to have genetic testing as a service this preferably should be done using a separate sample and following appropriate laboratory and clinical service standards. There may be exceptional situations when no service is available outside a research setting.

ANNEX A

POPULATION SCREENING

Genetic testing for late onset disorders currently takes place mainly in the context of a family history of a disorder, with healthy relatives already aware of their genetic risk and requesting testing to resolve it. The increasing identification of specific genetic changes means that it is now technically feasible to detect those at risk outside the family context, and simplication of technology allows genetic tests to be used for screening large groups, even whole populations, for the detection of mutations underlying late onset disorders.

The use of genetic tests for such screening raises important issues over and above those already identified for family based genetic testing, including the following:

(a) The procedures for sample collection and laboratory analysis may mean a greater error rate than when testing results from an individual request. This must be clearly recognised by all involved and confirmation of the initial screening result must be built into the programme.

(b) Those being screened will be likely to know less about the disorder, the test and its implications than those requesting testing because of family history. There is a particular need to ensure full understanding and support, yet the large numbers involved make it likely that this may not be adequately provided, or that it is restricted to those proving to have an abnormal result.

(c) Where a genetic test is used to screen populations of affected individuals to detect a genetic subset (e.g. screening all individuals with breast cancer for the BRCA1 mutation), those tested may not have been aware that the disorder was genetic in nature, with consequences to their relatives.

(d) Genetic screening raises more general screening, epidemiological and public health issues that need consideration along with the specifically genetic issues. These include that screening should only be introduced where an appropriate treatment (or follow-up action) is available and where treatment of the disorder at an early stage is of more benefit than treatment at a later stage.

(e) Appropriate support should exist to assist those who prove to have an abnormal test result. It is important to avoid prematurely "medicalising" healthy individuals.

(f) There is a potential conflict in genetic screening programmes between the aim of maximising choice for individuals and "public health" goals of reducing the

frequency of a genetic disorder. The aims of any screening programme should be made explicit.

(g) The National Screening Committee should be consulted about any recommendations on the introduction of screening programmes involving genetic testing.

ANNEX B

DIAGNOSTIC GENETIC TESTING

Until recently, most genetic testing neither aimed at nor permitted a specific diagnostic use. Most of the issues discussed above are relevant to the testing of healthy relatives at risk for a late onset disorder that has already been diagnosed and recognised as genetic in nature, in an affected family member.

The specificity of genetic mutations for an increasing number of late onset disorders now gives the possibility of a primary diagnostic use of genetic testing in patients showing clinical features thought possibly to be due to a particular genetic disorder, even though there may be no family history of this. This increasingly important use of genetic testing is becoming an important part of overall medical practice and has implications different from those for presymptomatic (predictive) genetic testing.

(a) Diagnostic genetic testing will principally be requested not by the individuals themselves, nor by specialists in genetics, but by a wide variety of medical staff in different clinical specialties and in primary care. Most will have little detailed knowledge of medical genetics and many will be unaware of the important issues outlined in this document and elsewhere.

(b) Individuals being diagnostically tested will be symptomatic; the test result will identify the nature of a disorder, rather than its presence or absence. However, the possible genetic nature of the illness may not be recognised by the person tested or by their relatives, and this should be made clear, and further information and support offered.

(c) Where a symptomatic patient is being investigated in the context of a family history of a late onset disorder, it is important to ensure that the clinical features support this diagnosis, or that other causes have been excluded as far as possible. If this is not done, an abnormal result may be obtained that is unrelated to the patient's symptoms. In effect a presymptomatic test will have been done, without the appropriate preparation and other measures.

ANNEX C

GENETIC SUSCEPTIBILITY

Genetic testing in clinical practice currently mainly concerns disorders following clear cut inheritance, determined by a single major gene. Most common disorders of later life however, do not show simple inheritance patterns, even though many are increasingly recognised as having an important genetic contribution to their pathogenesis. Common and serious late onset disorders in this group include diabetes, hypertension, coronary heart disease and susceptibility to various infectious agents. Current research is resulting in some of the specific genetic factors being identified, giving the possibility of genetic testing by DNA analysis.

At present, there is considerable uncertainty as to the extent of involvement of the specific genes in these common disorders. There may be variation between different studies or different populations, while the finding of association between a particular genotype and disease is rarely based on longitudinal study. The particular genetic changes involved often form part of normal variation in a population, unlike the rare and specific changes associated with single gene disorders.

Testable genetic factors in common diseases rarely show an absolute association, but may relate to susceptibility by indicating an increased or decreased likelihood of developing the disorder. There will be many individuals showing the genetic change who will not develop the condition and many others with the disorder who do not show the particular change. The strength of the association will vary, and will represent only one of a number of factors that collectively determine whether the disorder will develop.

Genetic susceptibility testing is thus very different in nature from conventional genetic testing for single gene disorders and will rarely be relevant to the usual indications for genetic testing in that group. However, there may be important reasons for testing being undertaken, particularly as our knowledge of the genetic basis of common diseases becomes better established. These include:

(a) Greater understanding of disease mechanisms. It may be possible to separate broad disease categories into more specific groups and this may be relevant to therapeutic approaches.

(b) Identification of genetic susceptibility to particular drugs could become important in drug choice and dosage.

(c) Identifying genetic susceptibility to infectious diseases could be relevant in targeting immunisation and related programmes.

(d) Those identified as being at high risk for common chronic disorders could adjust their diet, lifestyle and other factors to reduce the risk of developing the disorder.

At present, the evidence that individual genetic testing will give clear benefits in any of the above respects remains preliminary. It is thus important that clinicians, and the general public, are aware of this, and that they do not expect the same accurate predictive and diagnostic results as can now be obtained for many single gene disorders. Data on the scientific and clinical validity will be particularly important to establish, as well as evidence as to real benefit to these tested.

When genetic susceptibility testing for common late onset disorders does become established in clinical practice, it is likely that it will be applied in a very different way from the genetic tests established for clearly inherited disorders. It is unlikely that specialist genetics services will be significantly involved in the clinical and genetic counselling aspects; these, where necessary, are more likely to be dealt with by those involved in primary care and the relevant clinical specialties. Likewise the laboratory service patterns may well be different from existing genetic testing services; they may form part of more general laboratory services.

One subgroup of common late onset disorders requiring special attention is where a small proportion of cases prove to follow a clear single gene inheritance pattern. Important examples of this are seen in breast and colorectal cancer, where around 5-10% of cases are now known to be determined by specific genes of major effect, giving very high risks of disease in those with a particular genetic constitution. Separation of such subgroups from the much larger proportion of cases where the genetic risks are relatively small, has proved of considerable importance to those families detected with a specific change and allows genetic testing in them to be considered along the same lines as for rarer genetic disorders. It is likely that comparable clearly genetic subgroups will emerge in other common late onset disorders as their underlying basis becomes clearer.

ANNEX D

Members of the Advisory Committee on Genetic Testing (ACGT)

Rev Dr John Polkinghorne KBE FRS	Chairman
Professor Kay Davies *	Department of Biochemistry, Oxford.
Professor John Durant	Assistant Director, The Science Museum, South Kensington.
Professor Peter Harper *	Professor & Consultant in Medical Genetics, Cardiff.
Dr Hilary Harris	General Practitioner, Manchester.
Professor John Harris *	Professor of Bioethics & Applied Philosophy, University of Manchester.
Miss Wendy Johnston *	Genetic Health Visitor, Belfast City Hospital Trust
Mrs Christine Lavery *	Director of the Society for Mucopolysaccharide Diseases and founding trustee of the Genetic Interest Group.
Professor Sally Macintyre	Director, MRC Medical Sociology Unit.
Mr Matthew Parris	The Times.
Professor Marcus Pembrey	Mothercare Professor of Paediatric Genetics, Institute of Child Health, London.
Dr Sultana Saeed	Formerly Lecturer in Law, University of London.
Mr Philip Webb	General Manager, Zeneca Diagnostics, Abingdon, Oxfordshire.

* Members of the Late Onset Disorder Sub-Group.

ANNEX E

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Association of Clinical Cytogeneticists
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To promote the science and service of clinical cytogenetics, to ensure the development and maintenance of professional standards and to act as an advisory body on behalf of the profession.

Association of Genetic Nurses & Counsellors
Department of Clinical Genetics
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
Telephone: 0131 651 1012

The AGNC is one of the founding groups of the British Society for Human Genetics. Its role is to represent the interests of nurses and counsellors working in the field of genetics.

British Society for Human Genetics
Clinical Genetics Unit
Birmingham Women's Hospital
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Birmingham B15 2TG
Telephone: 0121 627 2630

The main academic and professional society for human geneticists. Includes all members of CGS, CMGS, ACC and AGNC, plus others.

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inical Molecular Genetics Society
egional Molecular Genetics Laboratory
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nical Molecular Genetics Society - part of the erated BSHG representing diagnostic molecular neticists mostly working in NHS Regional Genetics ntres.

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tanical Gardens
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A (UK) Ltd accreditation programme provides peer ew inspection of pathology departments to assess quality of service provided.

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vides advice and information to families caring for dren with disabilities, including inherited disorders.

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cliffe House, Water Lane, Wilmslow
eshire SK9 5AF
ephone: 01625 545745

Registrar promotes and monitors compliance with Data Protection Act 1984 which regulates the use of omatically processed personal information.

Genetic Interest Group
29-35 Farringdon Road
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GIG is the UK alliance of charities and support group for people who are affected by genetic disorders.

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Promotes the science and practice of pathology - th study of the cause and effect of disease - aims t increase public awareness of the broad scope pathology and its role in saving and protecting lives.

Royal College of Physicians
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Clinical Pathology Accreditation (UK) Limited, 45 Rutland Park, Botanical Gardens, Sheffield S10 2PB. Telephone: 0114 268 6151.

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CONSULTATION DOCUMENT - ONLY

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